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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,737	12/15/2005	Timo Heinrich	Merck-3100	1689

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
08/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,737	HEINRICH ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The double patenting rejections regarding applications 10/560734 and 10/539516 have been overcome by the amendment filed 4/23/08.

2. The rejection under 35 U.S.C. 101 has been overcome by the amendment filed 4/23/08.

3. The objections to the IDS have been overcome by the amendment filed 4/23/08.

4. As a result of the amended claim set, claims 1-4, 6-9, and 11-14 are currently pending.

Rejections Maintained / New Rejections based on Amended Claims

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 6-9, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and salts thereof, does not reasonably provide enablement for solvates of compounds of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants only show the preparation of the parent compounds and their salts. Applicants have not shown how to make and use any solvates of the parent compounds. Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26) teaches that the formation of solvates is unpredictable due to the unique nature of each compound in a series of related molecules (page 18, section 3.4, cited in previous office action).

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*,

858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds where an indole ring is connected to a piperazine or piperidine ring by C_{2-6}alkyl chain, and the piperazine or piperidine ring is connected to a benzo[*b*]furan ring by a C_{0-4}alkyl chain. Compositions comprising compounds of this formula are present as well as different methods of using these compounds.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26) teaches that the formation of solvates is unpredictable due to the unique nature of each compound in a series of related molecules (page 18, section 3.4).

(5) The relative skill of those in the art:

One of relative skill in the art is indicated by the reference cited to support the examiner's position. The person of skill in this art will have extensive experience in organic compound synthesis or and/or and advanced degree in organic chemical synthesis.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of salts and stereoisomers of compounds of formula I. However, the specification does not provide guidance for preparation of solvates of compounds of formula I.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-4, 6-9, and 11-14 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

This rejection is maintained because applicants have not provided sufficient data or evidence to support the assertion that their compounds can indeed make solvates.

7. Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of premenstrual disorders through inhibition of 5-HT and/or selective serotonin reuptake inhibitors, does not reasonably provide enablement for treatment of all disorders associated with these three receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Ross et al. (*Expert Opinion on Therapeutic Patents*, **2003**, *13(10)*, 1491-99) teach that treatment of premenstrual syndrome can be done through activation or inhibition of 5-HT receptors or selective serotonin reuptake inhibitors (section 3, pages 1494-95).

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states,

> "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of inhibiting different diseases associated with 5-HT or selective serotonin reuptake inhibitors.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Ross et al. (*Expert Opinion on Therapeutic Patents*, **2003**, *13(10)*, 1491-99) teach that treatment (but not prevention) of premenstrual syndrome can be done through inhibition of 5-HT receptors or selective serotonin reuptake inhibitors (section 3, pages 1494-95).

(5) The relative skill of those in the art:

Those of relative skill in this art are those with the level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art are MD's and PhD's or those with advanced degrees and the requisite degree of experience in therapeutic methods for treating central nervous system disorders.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the treatment of PMS.

However, the specification does not provide sufficient guidance for the treatment of the broad spectrum of diseases, disorders and conditions associated with the inhibition of 5-HT and/or selective serotonin reuptake receptors.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 11-13 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim(s) 11 is unclear as to its intended scope. Such claim language reciting inhibitory activity is generally used to denote a causative factor in determining the process by which a particular disease occurs. Determining whether a given disease responds or not to inhibition or activation of “5-HT” or “selective serotonin reuptake inhibitors” involves much experimentation since a negative response from one patient does not mean the drug isn’t useful as no drug has 100% effectiveness. Thus what “success rate” determines if a particular compound is effective and how many patients (and dosage regimens) need to be tested? Applicants cite (page 13, line 12 to page 15, line 2) many diseases that are associated with “5-HT” or “selective serotonin reuptake inhibitors”. The test for determining compliance with 35 USC 112, paragraph two, is whether applicants have clearly defined “their” invention not what may be discovered by future research as this type of claim language clearly requires.

11. Claims 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What alcohol protecting groups are being referred to in claim 4? Greene lists many types of protective groups for a hydroxyl group (*Protective Groups in Organic Synthesis*, **1999**, chapter 2 table of contents, pages 17-23). This rejection has not been overcome because applicants do not particularly point out any syntheses within the specification that show the use of an alcohol protecting group. Example 1 shows the use of a halogen leaving group, but no alcohol leaving/protecting group(s).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 3, 4, 6, and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 9, and 18 of copending Application No. 10/539516. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound claimed in copending application 10/481270 embraces by both the specified claims of both applications. On page 8 of the

specification of copending application 10/481270, form I of the compound is made by recrystallizing from acetone. In application 10/560737, the final product is being recrystallized from diethyl ether. Diethyl ether and acetone are considered analogous solvents because they are both polar aprotic solvents. Form I in application 10/481270 may be formed by using diethyl ether instead of acetone because of their similar natures. Thus this rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4, 6-9, and 11-14 rejected under 35 U.S.C. 102(b) as being anticipated by Bottcher et al. (US 5532241, published July 2, 1996, included in IDS). Bottcher et al. teach compounds of examples 4 and 9. Compositions of these compounds are taught as well (column 7, line 66-columhn 8, line 23). Example 1 anticipates claim 1 because variables attached to the applicant's core, specifically R_1 or R_2 is methoxy (OA, where A is an alkyl group), variable m is 4, X is N, n is 0, and R_3 is CH_2OH (CH_2R_4 where R4 is OH). Example 4 anticipates claim 1 because R_1 or R_2 is cyano (or nitrile), m is 4, X is N, n is 0, and R_3 is $C(O)NH_2$ all attached to applicant's core. Since claim 14 is a compound claim, it is also anticipated. Claim 3 is anticipated because compound A of claim 3 is the same as the product of example 4. Step C of claim 4 is anticipated because in column 7, lines 31-49, it is taught that the compounds can be converted to salts by treatment with acid. This rejection is maintained because both of these compounds have valid groups form compounds of instant claim 1.

Claims 11 and 13 are anticipated as well because it is stated these compounds are useful as 5-HT_{1a} agonists and serotonin reuptake inhibitors (column 1, lines 35-40). Claim 13 is anticipated because the compounds can be used as analgesics (column 1, lines 46-50).

16. Claims 1-3, 6-9, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bathe et al. (WO 02/102794, published 27 December 2003). Bathe et a. report a core structure in the abstract which anticipates applicant's compounds wherein R_1 is cyano, m is 4, X is N, and R_3 is $C(O)NH_2$. Compositions involving this compound are taught on page 25, lines 10-19. Since claim 14 is a compound claim, it is also anticipated. Claim 3 is anticipated because the structure taught is the species A of claim 3. This rejection is maintained because the compound in the abstract has valid groups form compounds of instant claim 1. Claims 11-13 are anticipated now because page 3, line 1, to page 4, line 12, teaches different methods of use for the compounds, which overlap with claims 11-13 of the instant application.

17. Claims 1-3, 6-9, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartoszyk et al. (WO 02/39989, published 23 May 2002). Bartoszyk et al. teach a compound in the abstract (2^{nd} line) where R_1 or R_2 is cyano, m is 4, X is N, and R_3 is $C(O)NH_2$ as a combined serotonin reuptake inhibitor and 5-HT_{1a} agonist. Compositions involving this compound are taught on from page 8, line 16 to page 10, line 10. Claims 11-13 are now anticipated as well because this compound is being used for the same method as the instant compounds. Since claim 14 is a compound claim, it is also anticipated. Claim 3 is anticipated because the compound is the same as species A of claim 3. This rejection is maintained because this compound contains valid groups for compounds of instant claim 1.

18. It is noted that Dorsch et al. (WO 02/083666, published 24 October 2002) is considered prior art. Compound ESI 499 (page 25) is considered prior art. Other examples of prior art that qualify under 35 U.S.C. 102 and/or 103 may exist in this reference as well.

Conclusion

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624